A novel Evans blue organic compound-appended PSMA-617 peptide as SPECT molecule imaging agent for human prostate LNCaP animal model

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<https://doi.org/10.17952/35EPS.2018.027>

Background

The PSMA-617 is a high binding affinity ligand for prostate-specific membrane antigen (PSMA) which is strongly expressed in prostate cancer and up-regulated in poorly differentiated, metastatic and hormone-refractory carcinoma compared with health tissue (1). To conjugate with albumin is a new method for improving the pharmacokinetic profile of peptides. We used a new R&D strategy that changed the linking site of tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid in PSMA-617 and modified with truncated Evans blue which was a good human serum albumin binder (2).

Method

The modified PSMA-617 was abbreviated to DOTA-EB-PSMA-617. The DOTA-EB-PSMA-617 were prepared by linking a truncated Evans blue to the lysine, attaching the DOTA chelator to the α -amine, attaching a maleimide to the ϵ -amine, and finally attaching thiolated PSMA-617 peptide to the maleimide. To determine radiolabeling parameters, the DOTA-EB-PSMA-617 (peptide amount 10-25 μ g) was labeled with ~6mCi indium-111 chloride (from INER, Institute of Nuclear Energy Research in Taiwan) in sodium acetate (NaOAc) with pH 6.0 at 95°C for different incubation time (5 to 20mins). The radiochemical purity (RCP) of In-111-DOTA-EB-PSMA-617 was qualified by radio-TLC with citric acid/ sodium citrate buffer. The solvent front was free indium-111 and the origin spot was In-111-DOTA-EB-PSMA-617. Then we used prostate carcinoma cells LNCaP (PSMA +) and PC-3 (PSMA-) to determine the *in vitro* bio-activity of radiolabeled products by cell binding assay. And we used LNCaP or PC-3 tumor bearing mice to determine the *in vivo* bio-distribution of In-111-DOTA-EB-PSMA-617 via nanoSPECT/CT.

Result

The radiochemical purity of In-111-DOTA-EB-PSMA-617 was greater than 95%. In cell binding assay, the peptide concentration of In-111-DOTA-EB-PSMA-617 was 2.5nM to 250nM and incubated for 45mins at 37°C. With the amount of treated peptide increase, there had been strong and higher radio-counts in LNCaP cells than PC-3 cells analyzed by γ -counter (Fig. 1). And we found that radio-activity accumulated in the LNCaP tumor site at 48 hours post-injection of 18.5MBq In-111-DOTA-EB-PSMA-617. There has longer circulating time of In-111-DOTA-EB-PSMA-617 compared with In-111-PSMA-617 (Fig. 2).

Conclusion

We altered the pharmacokinetic/pharmacodynamic (PK/PD) profile of PSMA-617 successfully by conjugating PSMA-617 with EB. And PSMA-617 modified with EB motif has potential to be a theranostics agent to change the therapeutic cycle of PSMA-617 in shorter time.

References

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